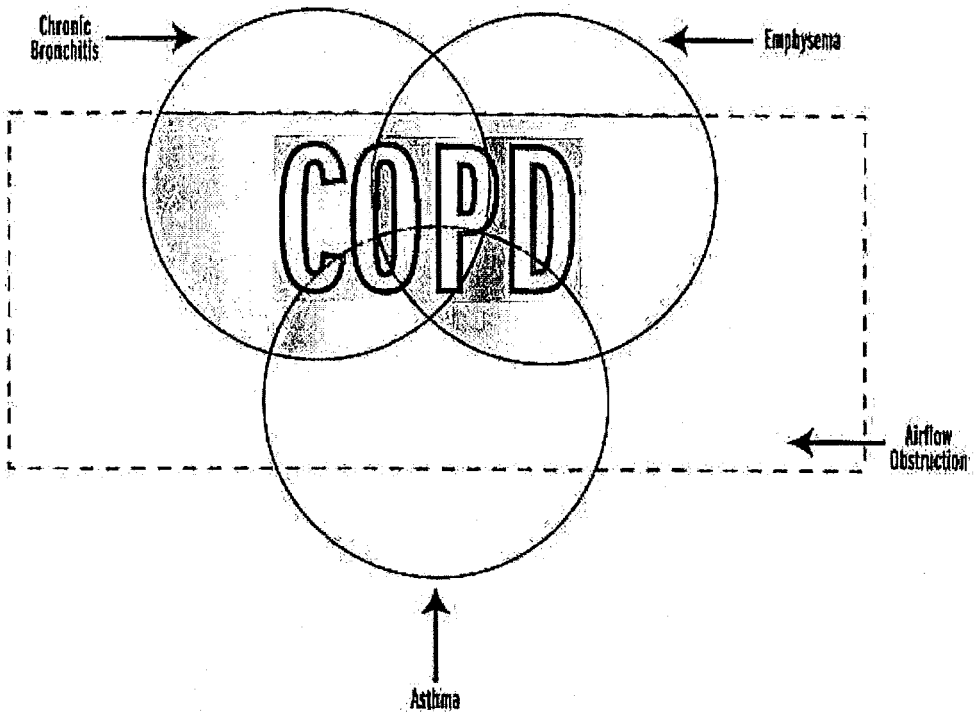
COPD and ASTHMA...

DIFFERENT diseases with SIMILAR symptoms



Adapted from American Thoracic Society.[1]

Diagnosis may be confusing, because many ASTHMA and COPD patients experience[2,3]:

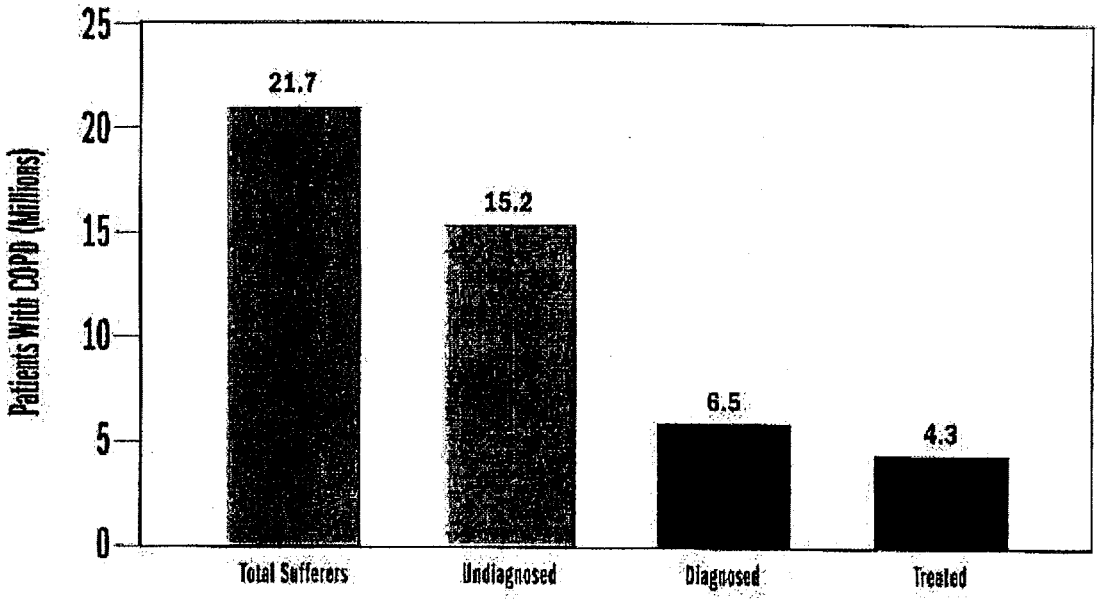
- Wheezing
- Dyspnea
- Sputum production
- Cough
- Frequent use of short-acting β_2-agonists

A diagnosis of COPD should include an assessment of exposure to risk factors, including[2]:

- Tobacco smoke
- Indoor/outdoor air pollution
- Occupational dusts and chemicals
- History of recurrent respiratory infection

Is COPD appropriately DIAGNOSED?

COPD—Too many patients undiagnosed[4]



Based on the Third National Health and Nutrition Examination Survey (NHANES III), 1988-1994.[4]

Why COPD is underdiagnosed[1,2]

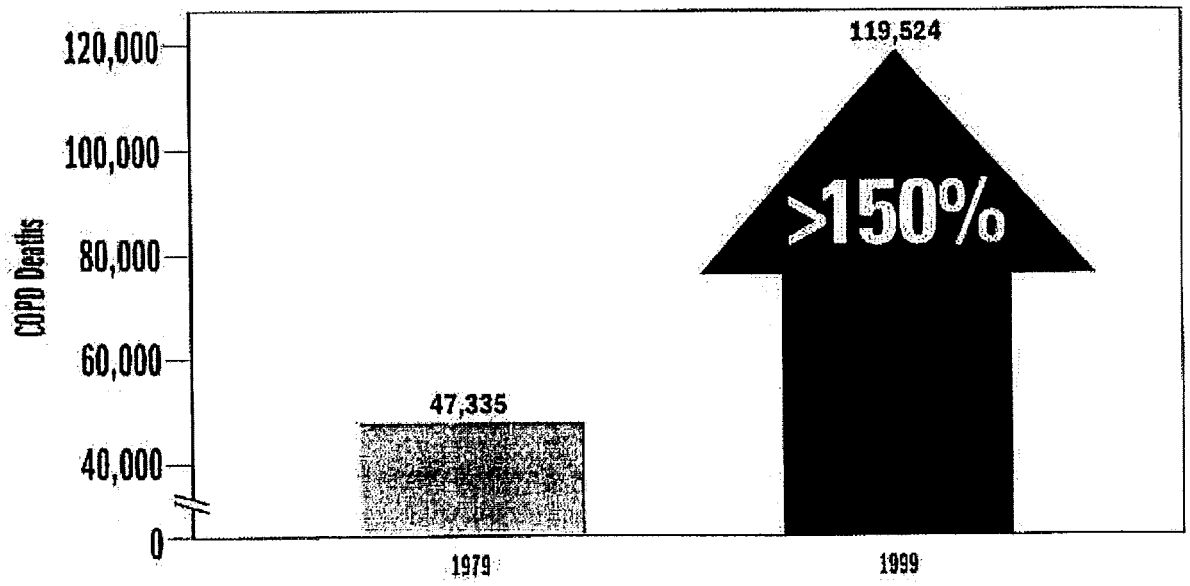
- Many patients do not recognize COPD symptoms such as cough, sputum production, and dyspnea as abnormal and do not seek treatment until late in the course of the disease[2]
- Spirometry, considered the gold standard for diagnosing and monitoring COPD, may not be readily available or used by physicians in some communities[2]
- Often it is not possible to differentiate asthma with incomplete reversibility of airflow obstruction from COPD with partial reversibility[1]

"Prevalence and morbidity data greatly underestimate the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced."

— GOLD Guidelines[3]

How has COPD CHANGED over TIME?

Total COPD deaths[5]



An increasing public health problem[5,6]

- Deaths among women rose by nearly 350%, and deaths among men rose by nearly 80%, from 1979 to 1999[5]
- COPD is the fourth-leading cause of death in the United States[6]
- Of the top causes of mortality, only COPD continues to rise[6]

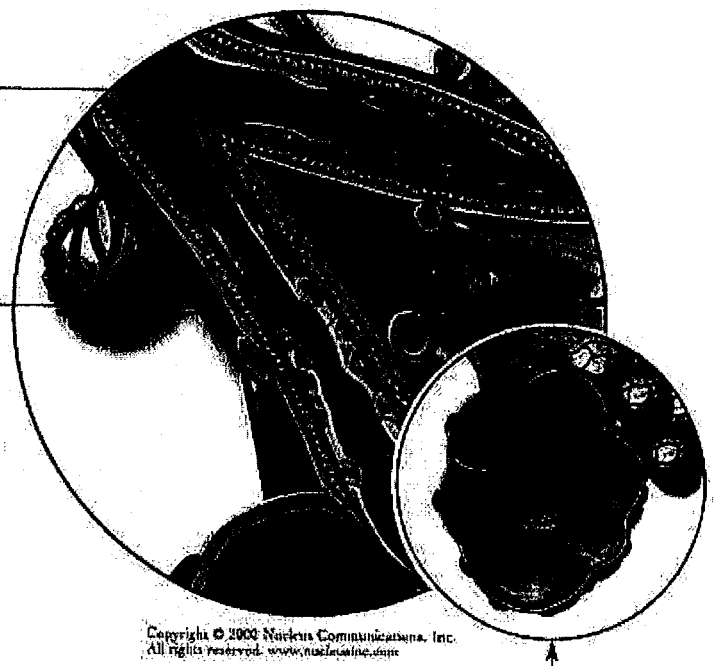
COPD—it's a disease of

MULTIPLE COMPONENTS

that result in airflow obstruction

Bronchoconstriction[2]

- Bronchoconstriction may be partially reversible in many patients with COPD
- Airway hyperresponsiveness may develop after exposure to tobacco smoke or other environmental insults
- Chronic inflammation is associated with an increase in the amount of smooth muscle in the airway wall



Inflammation[2]

- Although inflammation is important in both diseases, the inflammatory response in COPD is markedly different from that in asthma
- Neutrophils are important inflammatory cells in COPD and may contribute to tissue destruction and increased mucus production
- Airway eosinophils are increased during acute exacerbations, although their role in COPD is uncertain

Structural changes[2]

- Destruction of alveolar walls causes reduction in area for gas exchange and loss of elastic recoil (emphysema)
- Fibrosis of the small airways
- Epithelial changes include loss of cilia, increase in mucus-secreting cells, and degeneration of airway cartilage
- Vascular changes may lead to pulmonary hypertension

References: 1. American Thoracic Society. ATS Statement: Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1995;152(suppl, pt 2):S77-S120. 2. *Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: NHLBI/WHO Workshop Report.* Bethesda, Md: National Heart, Lung, and Blood Institute; National Institutes of Health; April 2001. NIH publication 2701. 3. National Heart, Lung, and Blood Institute. *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.* Bethesda, Md: National Institutes of Health; 1997. Publication 97-4051. 4. Data on file (analysis of data from Third National Health and Nutrition Examination Survey [NHANES III], 1988-1994); GlaxoSmithKline. 5. American Lung Association. *Trends in Chronic Bronchitis and Emphysema: Morbidity and Mortality.* Epidemiology & Statistics Unit. Best Practices and Program Services; March 2002. 6. Murphy SL. *Deaths: Final Data for 1998.* Hyattsville, Md: National Center for Health Statistics; 2000. National Vital Statistics Reports; 48(11).

GlaxoSmithKline

COPD disease awareness sales aid

Introduction

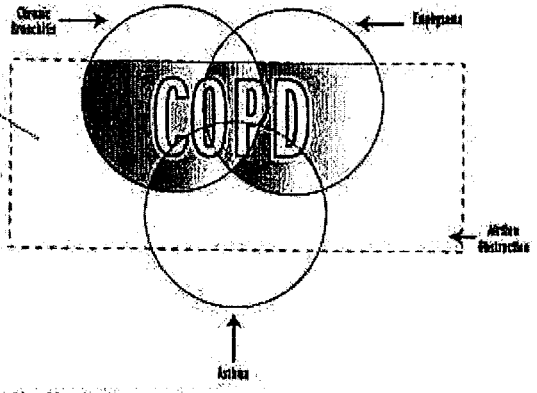
The goal of this sales aid is to communicate that the pathophysiology of COPD isn't as clearly defined as asthma, and is recognized as a disease of multiple components, including inflammation, bronchoconstriction, and tissue destruction. Its purpose is to educate physicians on COPD and the significant role these components play in the disease process.

The first page of the sales aid aims to show that although asthma and COPD are different diseases, there is an overlap because both diseases share similar symptoms. A clear diagnosis of COPD is important so that the disease may be treated effectively. Carefully assessing the patient's medical history, including exposure to certain risk factors, is a part of making the diagnosis of COPD.

- COPD and asthma have differences and similarities
- This Venn diagram, adapted from the American Thoracic Society, shows the relationship between asthma and COPD—there is some overlap among the diseases
- This overlap can lead to confusion, because patients with either disease may experience the same symptoms
- While smoking is the most common risk factor for COPD, there are others to consider as well

COPD and ASTHMA

DIFFERENT diseases with SIMILAR symptoms



Adapted from American Thoracic Society[1]

Diagnosis may be confusing, because many ASTHMA and COPD patients experience[2,3]:

- Wheezing
- Dyspnea
- Sputum production
- Cough
- Frequent use of short-acting β_2-agonists

A diagnosis of COPD should include an assessment of exposure to risk factors, including[2]:

- Tobacco smoke
- Indoor/outdoor air pollution
- Occupational dusts and chemicals
- History of recurrent respiratory infection

Proof Sources

American Thoracic Society
GOLD Guidelines

For internal use only.
Not be shown to or left with healthcare professionals.

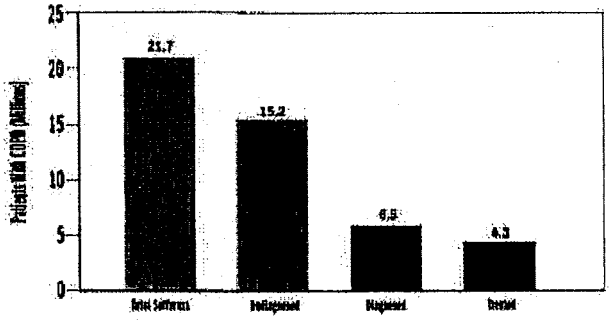
COPD disease awareness sales aid

Although diagnostic tools and criteria are in place, COPD is an underdiagnosed disease. This page is a call to action for better and earlier diagnosis.

- Of the 21.7 million patients with COPD, under 20% of those patients are treated —most likely because millions are not being diagnosed
- Underdiagnosis could result from a number of factors, including patients who don't seek treatment, physicians' limited access to or use of standardized spirometry, and the difficulty of differentiating COPD from asthma
- The GOLD Guidelines point out that the total burden of COPD is often misrepresented because of the problems diagnosing the disease in its early stages

Is COPD appropriately DIAGNOSED?

COPD—Too many patients undiagnosed[1]



Based on the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994[1]

Why COPD is underdiagnosed[1,2]

- Many patients do not recognize COPD symptoms such as cough, sputum production, and dyspnea as abnormal and do not seek treatment until late in the course of the disease[2]
- Spirometry, considered the gold standard for diagnosing and monitoring COPD, may not be readily available or used by physicians in some communities[2]
- Often it is not possible to differentiate asthma with incomplete reversibility of airflow obstruction from COPD with partial reversibility[1]

"Therefore, not surprisingly, this greatly underestimates the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced."
— GOLD Guidelines[1]

Proof Sources

American Thoracic Society
GOLD Guidelines

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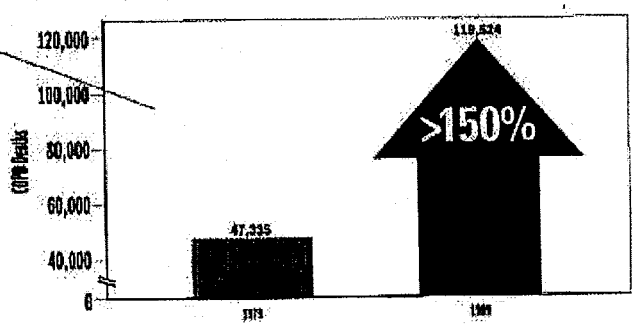
COPD disease awareness sales aid

This page validates the need for earlier and more accurate diagnosis. COPD is a growing and urgent public health concern that needs to be addressed through education and diagnosis.

- The burden of COPD has increased over the last 20 years
- The total number of COPD deaths in the United States increased 150% from 1979 to 1999
- The public health burden of COPD is still on the rise—it's currently the fourth leading cause of death in the United States, and death rates continue to increase

How has COPD CHANGED over TIME?

Total COPD deaths[5]



An increasing public health problem[5,6]

- Deaths among women rose by nearly 360%, and deaths among men rose by nearly 80%, from 1979 to 1999[5]
- COPD is the fourth-leading cause of death in the United States[6]
- Of the top causes of mortality, only COPD continues to rise[6]

Proof Sources

American Lung Association
Murphy Study

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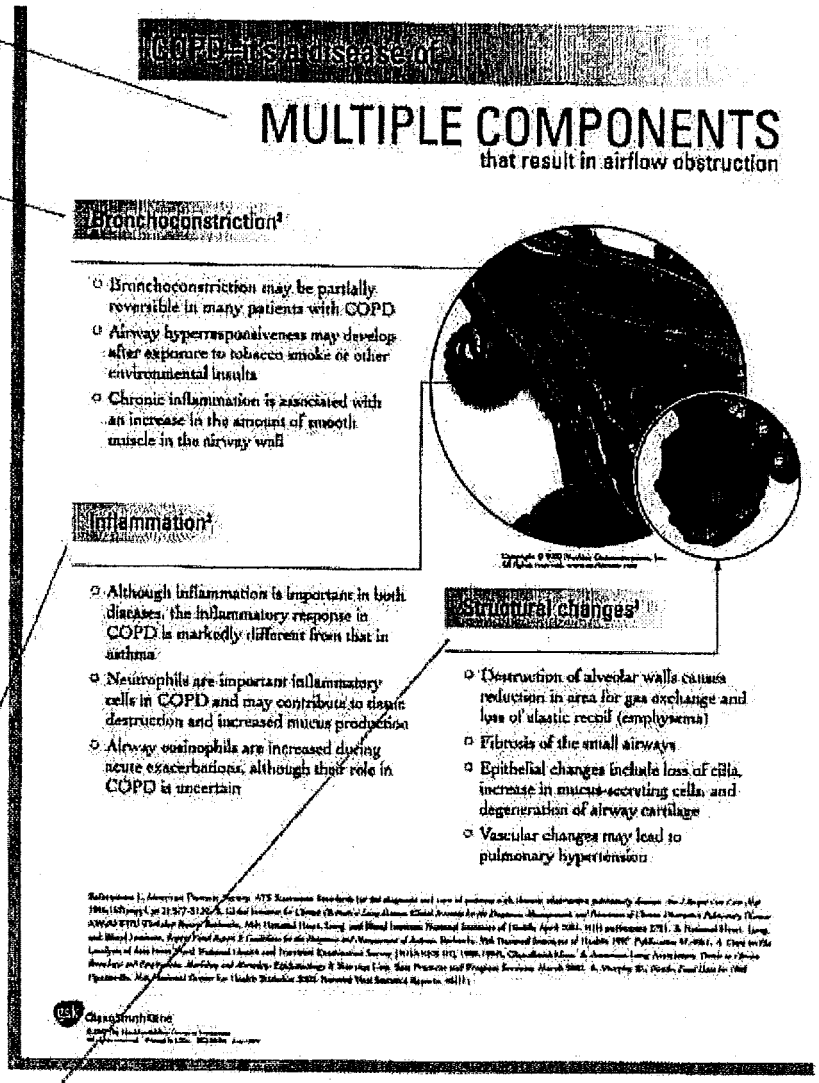
COPD disease awareness sales aid

This page reinforces the roles that bronchoconstriction, inflammation, and structural changes play in COPD.

- COPD is a complex disease with many components
- Physicians recognize bronchoconstriction as a major component of COPD
- Environmental insults (like tobacco smoke or other noxious chemicals) can lead to hyperresponsiveness and bouts of wheezing, coughing, and shortness of breath, which may sometimes be severe enough to cause an exacerbation
- Bronchoconstriction and inflammation overlap —chronic inflammation increases the amount of smooth muscle in the airway wall, narrowing the passageways. Increased sputum may also block airways
- Physicians may not be aware that inflammation plays a role in COPD
- The inflammatory response differs in COPD and asthma
- Inflammation in asthma is mainly eosinophilic; in COPD, it is mainly neutrophilic



- Tissue destruction also leads to airflow obstruction, and many of the structural changes are irreversible. This highlights the need for earlier diagnosis
- Pulmonary hypertension develops in the late stages of COPD and has a poor prognosis

For internal use only. Not be shown to or left with healthcare professionals.

Proof Source
GOLD Guidel

eFORCE

Enrolling in the COPD Learning System Courses in eFORCE

Note: There are three courses in eFORCE for the first Module in the COPD Learning System **(COPD Learning System: Module1, course 1-3**

Connecting to eFORCE:

- Connect to the network via SFA dialer (check either **Quick Connect** or **Remain Connected**). If you select **Remain Connected** please wait until file transfers are complete before using eFORCE.
- From your desktop, double-click the **eFORCE Online** icon. (Or select it from the Start menu.)
- At the **Enter Network Password** prompt, enter your User Name and Password. This is the same User Name and Password you use to log on to your computer.

Completing an Activity:

- From the eFORCE course catalog, click the **Science** sub-catalog.
- Depending on which course you would like to enroll in, click either **COPD Learning System: Module 1, course 1,2, or 3 (all 3 courses must be completed and it is suggested that you take them in order.**
- You may complete the course online or in eFORCE Mobile (offline). Once you choose, you **must** complete it in that mode. Consider the pros and cons of each:

	Pros	Cons
Online	Simple process	• Performance may be slow if connection (modem) speed is low or if intranet traffic is high • Less flexibility in choosing where to complete the course (because you must be near a phone jack) • Ties up phone line
Offline	• Performance may be faster • More flexibility in choosing where to complete the course • Keeps phone line free	• Multi-step process to enroll in the course

To complete online:

- Click **Enroll Online**, then click **Enroll** to confirm your selection.
- Click **Enter the course.**
- Follow the on-screen instructions to complete the course.

To complete offline:

Completing a course offline is a 3-step process: (1) Download (2) Complete (3) Sync.

1. Download

- Click **Enroll in Mobile**, then click **Enroll** to confirm your selection.
- Click **Enter the course** to launch eFORCE Mobile.
- Click the link called **Download module COPD Learning System: Module 1, Courses 1, 2, or 3.** The program will now download the module to your computer.

- When it is complete, eFORCE Mobile will launch the module. However, don't take it now (you want to get offline first). Close the Mobile window, close your Internet Explorer window, and terminate your remote connection.

2. **Complete the module**
   - Double-click the **eFORCE Mobile** icon on your desktop.
   - Click on the **COPD Learning System** course from the list.
   - Follow the on-screen instructions to complete the course.
   - **After completing he course you will be directed to a summary page, which confirms that you have completed the course. This summary page must be printed out and sent to your DSM for verification. You will be unable to receive credit and receive notice that you have completed the program until you have visited each tab on each page of the course (including key points)**

Sync results

- Reconnect to the network and double-click on the **eFORCE Online** icon.
- Click **My Transcript**.
- Click the **Enter the Course** link in the **Learning Activities in Progress** section.
- Click **Sync your results**.
- Click **Click here to send your results back to the CDS**.
- Click **Logout to LMS**.

After you have completed the course (and sync'd your results, if necessary), you'll see it listed My Transcript in the Learning Activities Completed section.

Help Desk

For technical support with eFORCE, contact the Sales Support Center at 1-800-830-8204.

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MEMO

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PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709

Tel: 919 483 2100
www.gsk.com

To Respiratory PSRs, TS, DSMs, RTs, MDMs, RVPs

From COPD Sales Training and Marketing

Date October 21, 2003

CC Ken Lowry, Simon Jose

Subject COPD Pre - Launch Training

The ADVAIR COPD product team is excited to launch an updated COPD training plan (including revised learning modules) that is designed to enhance your COPD disease area knowledge and enable you to become a greater resource to your customers after approval. As you may know, the COPD marketplace is characterized by a large number of diagnosed patients (10.5 MM) with approximately 17MM prescriptions written per year. Currently almost 40% of patients treated for COPD are prescribed 2 or more controllers.

Over the next 3 months, you will receive 3 COPD manuals and take 3 eFORCE exams (one for each manual). By working hard to complete these manuals, you will be prepared - upon approval - to make an immediate impact in your territories by selling this new indication with confidence and passion.

The COPD learning resource system will consist of 3 manuals:

Manual 1: COPD Background and Overview

****NEW AND IMPROVED**** - Includes in-depth discussion about the anatomy, pathology, and pathophysiology of COPD including rationale for treating both the inflammation and bronchocontriction of COPD.

Manual 2: Clinical Rationale for Treatment of COPD with ADVAIR DISKUS®

****NEW**** - Includes recently published data supporting the use of ADVAIR for the treatment of COPD and new comparative data demonstrating superior lung function vs.Combivent

Manual 3: Selling ADVAIR DISKUS® in COPD

****FIRST EVER**** - To include Selling Messages, ADVAIR COPD label information, Competition, and Responses to commonly asked questions.

Due to an aggressive launch timeline, we need you to work hard and come out of the gates strong. With that in mind, following is the timeline for the receipt and completion of the COPD learning manuals:

Learning Manual:	Date of Receipt:	eFORCE window:	Completion date:
Manual 1	Week of 10/20	10/20-10/31	11/7
Manual 2	TBD (November)	TBD	TBD

Manual 3	TBD (December)	TBD	TBD

**Dates for shipment and completion of Manuals 2 and 3 will be communicated in the near future.

Upon completion of each manual, you will be required to take Advair COPD Learning exams. Once the individual exams are posted on eFORCE, you will need to complete each during their respective posting dates. After taking each exam, you will want to follow the simple instructions on how to submit exam results.

These three Advair COPD eFORCE exams **WILL NOT** be timed for their individual completion, however, you will be expected to achieve a score of 85% or greater on each exam.

On or around November 27th, we are expecting to hear from the FDA regarding the approval of Advair for the treatment of COPD. PLEASE **NOTE: UNTIL ADVAIR DISKUS IS APPROVED BY THE FDA FOR COPD, YOU MAY NOT DISCUSS OR PROMOTE THE PRODUCT FOR THIS INDICATION WITH HEALTHCARE PROFESSIONALS. TRAINING MATERIALS ARE BEING PROVIDED TO YOU IN ADVANCE SOLELY FOR THE PURPOSE OF PREPARING YOU FOR THE PRODUCT'S APPROVAL.**

If you do not receive your materials by the dates listed, please contact Mike Chorba at Docusource. His contact # is 919-459-5909

We want to thank you in advance for your participation and hope you enjoy learning the latest information surrounding Advair for COPD. Good Selling!

Contact Report

Date : 02/11/02
Name : ELLIS, JAMES H
Seen At : 1400 JACKSON ST
DENVER, CO 80206 2761

Territory : 00QI - DENVER TS
Cont.Type : Call
Status : Sent

[PRODUCTS DETAILED]

Primary : ADVAIR DISKUS INH PWDR
SEREVENT COPD
Secondary : None
Reminder : None

[SAMPLE DROP]

ReferenceNo.: ACPD060241

Sample Description	Qty
ADVAIR DISKUS INH PWDR 100/50MCG 28D	7
ADVAIR DISKUS INH PWDR 250/50MCG 28D	13
ADVAIR DISKUS INH PWDR 500/50MCG 28D	13
FLONASE 50MCG 50D 1'S	18
FLOVENT INH 220MCG 60D 1'S	24
SEREVENT INH AEROSOL 60 ACTN SPL 6.5	24

[NOTES]

Likes Advair for tx of copd. Asked him to go the Chicago meeting. said he will consider and get back to me.

Plan : F/U with Email and get commitment by thrus

Territory #:03UH
User Name : HAMRICK, BLAIR

Contact Report

Printed 07/31/03 08:36PM

Date : 02/26/02
Name : WEISS, STEVEN M
Seen At : 1721 E 19TH AVE
STE 366
DENVER, CO 80218

Territory : 04WD - NORTHERN COLORADO TS
Cont.Type : Call
Status : Sent

[PRODUCTS DETAILED]

Primary : ADVAIR DISKUS INH PWDR
AUGMENTIN ADULT
Secondary : SEREVENT COPD
Reminder : None

[SAMPLE DROP]

ReferenceNo.: AABB117488

Sample Description	Qty
ADVAIR DISKUS INH PWDR 100/50MCG 28D	5
ADVAIR DISKUS INH PWDR 250/50MCG 28D	10
ADVAIR DISKUS INH PWDR 500/50MCG 28D	7
AUGMENTIN TABS 875MG 1X2 PKR	30
FLOVENT INH 110MCG 60D 1'S	4
FLOVENT INH 220MCG 60D 1'S	9
FLOVENT INH 44MCG 60D 1'S	9
SEREVENT DISKUS INH PWDR SPL 28 CT	5
SEREVENT INH AEROSOL 60 ACTN SPL 6.5	8

[NOTES]

matz, like exacerbation data, we will look at these parameters for copd studies also. is using adv in copd. discussed diff in devices between diskus, turbohaler and foradil device. showed prime study and how there is advantage to diskus, reproduciability of dose compared to others.
augmentin they like it alot happy to get samples.

Territory #:03UH
User Name : HAMRICK, BLAIR

Contact Report

Printed 08/20/03 06:17PM

Date : 05/22/02
Name : ELLIS, JAMES H
Seen At : 1400 JACKSON ST
DENVER, CO 80206 2761

Territory : 00QI - DENVER TS
Cont.Type : Call
Status : Sent

[PRODUCTS DETAILED]

Primary : ADVAIR DISKUS INH PWDR
Secondary : None
Reminder : None

[SAMPLE DROP]

ReferenceNo.: ACPD063807

Sample Description	Qty
ADVAIR DISKUS INH PWDR 250/50MCG 28D	10
ADVAIR DISKUS INH PWDR 500/50MCG 28D	10

[NOTES]

superior symptom control. he said he feels his copd patients benifit from it.

Territory #:03UH
User Name : HAMRICK, BLAIR

Contact Report

Printed 08/20/03 06:16PM

Date : 03/21/02
Name : ELLIS, JAMES H
Seen At : 1400 JACKSON ST
DENVER, CO 80206 2761

Territory : 00QI - DENVER TS
Cont.Type : Call
Status : Sent

[PRODUCTS DETAILED]

Primary : ADVAIR DISKUS INH PWDR
Secondary : None
Reminder : None

[SAMPLE DROP]

ReferenceNo.: ACPD062566

Sample Description	Qty
ADVAIR DISKUS INH PWDR 250/50MCG 28D	7
ADVAIR DISKUS INH PWDR 500/50MCG 28D	10

[NOTES]

Discussed the use of ics inb copd with regards to prevednting re admission to a hosptial and overall mortality. Believres the data anbd his a big promponent of ics in both asthma and copd

Contact Report

Date : 04/12/02
Name : PLUSS, WILLIAM T
Seen At : 4567 E 9TH AVE
740
DENVER, CO 80220 3908

Territory : 04WD - NORTHERN COLORADO TS
Cont.Type : Call
Status : Sent

[PRODUCTS DETAILED]

Primary : ADVAIR DISKUS INH PWDR
Secondary : None
Reminder : None

[NOTES]

committed to 1 king prog, think of ics in asthma and copd

Territory #:03UH
User Name : HAMRICK, BLAIR

Contact Report

Printed 08/20/03 01:44PM

Date : 07/03/02
Name : SWEENEY, NINA K
Seen At :

Territory : 019U ~ ROANOKE
Cont.Type : Call
Status : Sent

[PRODUCTS DETAILED]

Primary : ADVAIR DISKUS INH PWDR
FLONASE
Secondary : None
Reminder : None

[SAMPLE DROP]

ReferenceNo.: CHNJ005656

Sample Description	Qty
ADVAIR DISKUS INH PWDR 500/50MCG 28D	5
FLONASE 50MCG 50D 1'S	18

[NOTES]

Asked for 500/50 for indigent patient. Told her about our programs and still asked. Using a lot of Advair said that she switched a patient who was on Pulmicort and Serevent to Advair. She said the pulmologist put the patient on those. Also told her good reason to use both Advair and Flonase is low systemic bioavail. She then told me she sees more COPD than asthma and asked for information. Sending her faxbk 428.

Territory #:03UH
User Name : HAMRICK, BLAIR

Contact Report

Printed 08/20/03 01:42PM

Date : 07/24/02
Name : SWEENEY, NINA K
Seen At :

Territory : 019U - ROANOKE
Cont.Type : Call
Status : Sent

[PRODUCTS DETAILED]

Primary : ADVAIR DISKUS INH PWDR
FLONASE
Secondary : None
Reminder : None

[SAMPLE DROP]

ReferenceNo.: CHNJ006069

Sample Description	Qty
ADVAIR DISKUS INH PWDR 250/50MCG 28D	10
FLONASE 50MCG 50D 1'S	12

[NOTES]

Said she is using more Advair went over the Fxbk and benefit to patient with COPD.

Territory #:03UH
User Name : HAMRICK, BLAIR

Contact Report

Date : 09/30/02
Name : CITRON, DANIEL C
Seen At : 4545 E 9TH AVE
STE 670
DENVER, CO 80220 3918

Territory : 00P4 - DENVER EAST
Cont.Type : Call
Status : Sent

[PRODUCTS DETAILED]

Primary : ADVAIR DISKUS INH PWDR
SEREVENT DISKUS/COPD MARKET DEVELOPMENT
Secondary : None
Reminder : None

[NOTES]

Advair core message COPD market development, he is really positive about adavir

Territory #:03UH
User Name : HAMRICK, BLAIR

Contact Report

Printed 08/20/03 02:13PM

Date : 01/15/03
Name : MOORE, NATHANIEL J
Seen At : 8200 E BELLEVIEW AVE
GREENWOOD VILLAGE, CO 80111 2803

Territory : 00N6 - DENVER SOUTH
Cont.Type : Call
Status : Sent

[PRODUCTS DETAILED]

Primary : ADVAIR DISKUS INH PWDR
FLONASE
Secondary : None
Reminder : None

[SAMPLE DROP]

ReferenceNo.: CBXP047872

Sample Description	Qty
ADVAIR DISKUS INH PWDR 100/50MCG 28D	4
ADVAIR DISKUS INH PWDR 250/50MCG 28D	4

[NOTES]

called for advair samples - copd cme invitation.

TO: Respiratory Sales Representatives with responsibility for COPD

CC: COPD Product Management

FROM: Bob Hastings, Product Manager, COPD Marketing

DATE: 11/27/02

SUBJECT: *"Building a COPD Care Plan" Interactive Voice Response (IVR) Program*

The COPD Marketing Team is happy to offer a unique opportunity for primary care physicians, physician assistants, nurse practitioners and retail pharmacists to participate in a taped interactive Continuing Medical Education telephone program sponsored through an educational grant from GSK. There will be two different programs. One presented for the actual provider on recognizing and diagnosing of COPD and the second program from the retail pharmacists perspective on understanding COPD and being able to counsel patients on COPD medications. The program will provide information pertaining to the management of and treatment options for COPD, including acute exacerbations and stable COPD, as well as similar or co-morbid disease states since the management of these conditions can be different.

This program is hosted by Sidney Braman, M.D., an internationally recognized authority on the diagnosis and treatment of COPD. Dr. Braman is a Professor of Medicine at Brown Medical School as well as Chief of Pulmonary and Critical Care Medicine at Brown Medical School and Rhode Island Hospital. His research and academic interests are primarily related to COPD and asthma and the investigation of new approaches to the treatment of airway disease and acute and chronic respiratory failure.

PROGRAM DETAILS

What is in this mailing?

- 50 invitations for primary care physicians, physician assistants and nurse practitioners.
- 50 invitations for retail pharmacists.

What is a CME Interactive Voice Response (IVR) program?

- IVR's provide physicians and other healthcare professionals the opportunity to obtain CME and CE at their convenience through a pre-recorded presentation.
- The two taped programs can be dialed into 24 hours a day, 7 days per week.
- The programs are available to physicians, NP's and PA's for three months starting December 2, 2002 through February 28, 2003.
- The physician, NP and PA program lasts approximately 30minutes and the retail pharmacist program lasts approximately 60 minutes. There are 5 CME questions at the end of the program along with program evaluation questions the doctor and pharmacist must answer to receive one hour of CME credit.
- Once the healthcare provider has called into the program they will receive instructions on navigating by phone through the program.

What is the topic of this IVR program?

The program discusses incorporating current guideline recommendations (GOLD) into everyday clinical practice, which requires the clinician to differentiate between acute exacerbations and stable COPD, as well as similar or co-morbid disease states since the management of these conditions can be different

Actions Required

- Introduce the CME program topic and provide the IVR invitation to your primary care physicians, nurse practitioners, physician assistants and the CE program to your retail pharmacists while making calls on these healthcare professionals.
- Inform the healthcare providers of the convenience of participation in this program sponsored by GSK and that it is accessible 24 hours a day, 7 days a week.
- Inform healthcare providers that the program will run through February 28, 2003.
- Details on participation by healthcare professionals and dial in number are located within the sealed brochure
- **Do not utilize invitations in product discussions, to respond to questions or for detailing purposes.**
- **Under the ACCME guidelines, sales representatives may not promote Advair® for unapproved indications such as COPD. If a physician has questions about Dr. Braman's presentation, please write them down and submit them to Leslie Bonino at lbonino@intellyst.com She will then forward then on to Dr. Braman for his comments.**

The success of this program depends on your participation! We know that the content and format of this program will be well received by your healthcare providers. Please make every effort to take advantage of this activity. Questions regarding this program should be directed to your district sales manager.

The Marketing Team for COPD

Lit ALERT

CLINICAL DEVELOPMENT & MEDICAL AFFAIRS - NORTH AMERICA

(from the Medical Information Department)

The TRISTAN Study (SFCB3024): Advair Diskus 500/50 in COPD

Advair/COPD

February 2003

CITATION: Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2003;361:449-456.

KEY MESSAGES:

- In patients with COPD, Advair Diskus 500/50 BID significantly:
  - improved lung function (FEV_1 and other lung function measures)
  - reduced exacerbations (that required oral corticosteroids or antibiotics)
  - improved symptoms (breathlessness)
  - reduced the use of rescue albuterol
  - improved health status
- Advair Diskus is not currently approved for the treatment of COPD in the U.S.

STUDY DESIGN

- This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, 1-year trial. This was the pivotal trial for the COPD indication in Europe.
- The primary efficacy measure was pre-dose FEV_1. Secondary measures of efficacy included other lung function measurements, exacerbations, symptoms, and health status.
- Patients received Advair 500/ 50, salmeterol 50 mcg, fluticasone propionate 500 mcg, or placebo each via the Diskus device twice daily.

PATIENTS

- 1465 patients with COPD were randomized to treatment. The mean age was about 63 years, about 75% of the patients were male, and the mean predicted FEV_1 was about 44%. These patients had poor reversibility to albuterol – mean of 4% increase in FEV_1
- All patients had at least 1 episode per year of acute COPD symptom exacerbation in the previous 3 years and at least one exacerbation in the year prior to study entry requiring oral corticosteroids or antibiotics.

RESULTS

- **FEV_1:**
  - Advair Diskus 500/ 50 provided a significant ($p< 0.0001$) increase in pre-dose FEV_1 that was evident within 2 weeks and was sustained throughout treatment compared with placebo. With Advair Diskus 500/ 50, the FEV increased by 133 mL more than placebo ($p< 0.0001$).
  - The increase in FEV_1 was statistically significantly higher with Advair Diskus than with FP ($p< 0.0001$) or salmeterol ($p< 0.0001$).
  - The same trends in improvements of treatment versus placebo were seen for other lung function measurements such as FVC and PEF.
- **Exacerbations:**
  - The rate of exacerbations fell by 25% in the Advair Diskus 500/ 50 group ($p< 0.0001$) compared with placebo.
  - **Acute exacerbations requiring oral corticosteroids or antibiotics were reduced by 39% in the Advair Diskus group ($p<0.0001$) compared with placebo.**
- **Symptoms.** Advair Diskus 500/ 50 significantly reduced symptoms of breathlessness and significantly reduced the use of rescue albuterol compared with placebo, FP, or salmeterol.
- **Health Status:** Only the Advair Diskus 500/ 50 group showed a clinically significant improvement from baseline in health status.
- **Adverse Events:** All treatments were well tolerated, and there were no differences between groups in the number of patients reporting an adverse event. Adverse events were similar across treatment groups except for oropharyngeal candidiasis (placebo 2%, salmeterol 2%, FP 7%, Advair 8%).

CONCLUSIONS

The authors concluded that treatment with Advair produced better control of symptoms and lung function with no greater risk of adverse events than that with use of either FP or salmeterol alone. Therefore, Advair Diskus is an effective treatment option for many patients with COPD.

COMMENTS

- TRISTAN is the largest and longest Advair Diskus COPD study to date.
- The increase in pre-dose FEV_1 of 133 ml seen with Advair Diskus 500/ 50 can be considered clinically significant.
- The maintenance of bronchodilator effects with Advair Diskus (and salmeterol) throughout the 1-year treatment period demonstrated that tolerance/ tachyphylaxis did not develop.
- In the accompanying editorial *(Rennard SI. COPD: treatments benefit patients. Lancet 2003:361:XXX-XXX),* Dr. Stephen Rennard stated that, " TRISTAN ...specifically evaluated the group least likely to show improvement [because the patients were selected for their lack of reversibility after albuterol] . That therapy helped is encouraging not only for the study participants, but also for the majority of COPD patients who seemingly are more likely to benefit from treatment."
- Although no strength of Advair Diskus is currently approved for COPD in the U.S., GSK has received an approvable letter from the FDA for Advair Diskus 250/ 50. Advair Diskus 500/ 50 has recently been approved for COPD in Europe, partially based on data from this trial.
- Data from the TRISTAN study, along with data from studies SFCA3006 (Mahler) and SFCA3007, are presented in FaxBack #428.

Call
1-888-825-5249

Fax
1-888-452-9611

Optimizing Care of the COPD Patient: Current and Future Directions

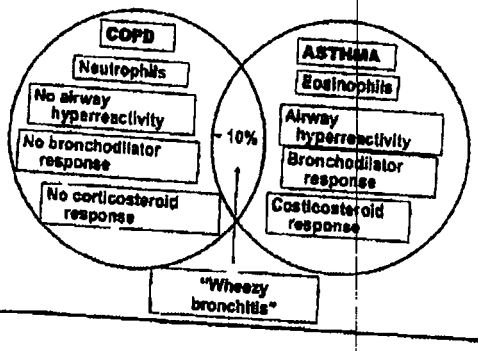
•Ron Balkissoon M.D. FRCPC DIH MSc.
•Associate Professor of Medicine
•National Jewish Medical & Research Center
•University of Colorado Health Sciences Ctr.

Impact of COPD

- Affects 16 to 30 million in US [1,2]
  - Approximately 1 in 10 Americans over age 65 [3]
- 110,000 deaths annually
- 14 million have primarily chronic bronchitis
- Fourth leading cause of death [2]
- Annual cost about $32 billion
  - 75% of direct costs related to exacerbations
- Impact of COPD rising while others falling

[1] Petty TL. J Respir Dis. 1997;18:355
[2] NHLBI. Morbidity & mortality: chartbook on cardiovascular, lung, and blood diseases. 1998
[3] Mannino DM, et al. Arch Intern Med. 2000;160:1683

OVERLAP BETWEEN COPD AND ASTHMA



COPD vs Asthma

•COPD	•Asthma
•Cell Types:	•Cell Types
•Neutrophils	•Eosinophils
•CD-8 Lymphocytes	•CD-4 lymphocytes
•Macrophages	•Mast Cells
•Mediators:	•Mediators:
•IL-8	•IL-4
•LTB-4	•IL-5
•TNFα	•IL-13

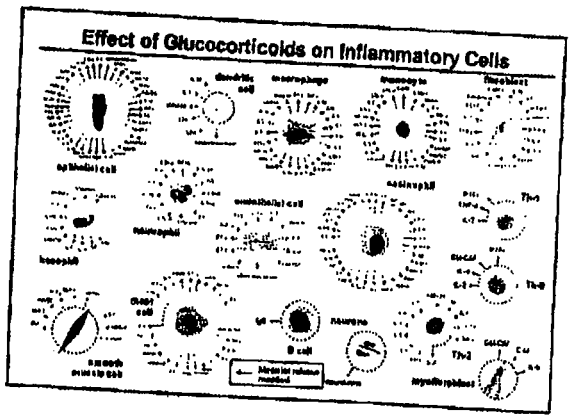
How Might COPD Patients Improve with Inhaled Corticosteroids?

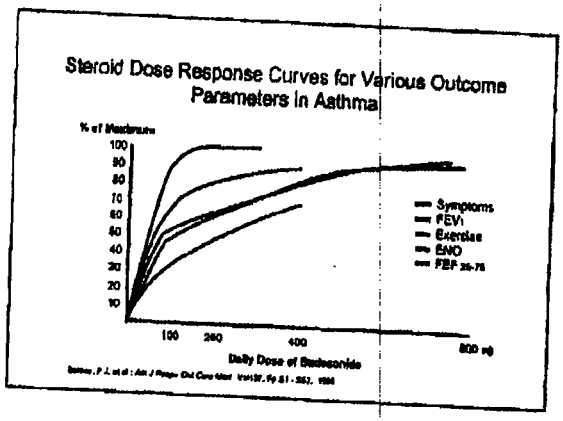
- Improvement in pulmonary physiology:
  - FEV_1, FVC, peak flow, inspiratory capacity, 6 minute walk
- Improvement in quality of life
  - Dyspnea indices
  - exercise performance
  - symptom scores
- Reduced need for rescue bronchodilators
- Reduced number of exacerbations (PCP, ER, consultant visits

GOLD: COPD Treatment

Stage		FEV_1	Treatment
0	At Risk	Normal	Avoid risk. Vaccinate.
I	Mild	$FEV_1 \geq 80\%$	Add short-acting bronchodilator prn
IIA	Mod	$80\% > FEV_1 \geq 50\%$	Add ≥ 1 regular bronchodilator
IIB		$50\% > FEV_1 \geq 30\%$	Consider inhaled steroids Add rehabilitation
III	Severe	$FEV_1 < 30\%$	Consider oxygen Consider surgery

What's the evidence?





INHALED STEROIDS IN COPD

	n	Sev	Dose, ug	Dur
Plaggiaro	281	mild -mod	1000 flut.	6 mo
Copenhagen	290	mild -mod	1200 - 800 bdp.	3 yr
EUROSCOP	1277	mild	800 bdp.	3 yr
ISOLDE	751	mod -sev	1000 flut.	3 yr
Lung Health	1116	mild -sev	1200 triam.	3 yr

EUROSCOP.

Pauwels RA. NEJM 1999; 340: 1948

- 39 centers in 9 European countries

Entry criteria:

- smoking 5 p.y. or 10 yr
- Current smokers after smoking cessation program (10% success)
- FEV1 50-100% pred
- < 10% reversibility
- FEV1/FVC < 70%

EUROSCOP.

Pauwels RA. NEJM 1999; 340: 1948

- Study Group:
- 912/1277 completed pts;
- FEV1 76% pred

- Rx:
  - Budesonide 800 ug daily x 3 years
  - vs
  - placebo

EUROSCOP

Pauwels RA. NEJM 1999; 340: 1948

- In the first 6 months, FEV_1:
  - Increased for budesonide
  - Decreased for placebo ($P < .001$).
- After 6 months,
  - parallel deterioration in FEV_1
- No data reported on exacerbations

Pauwles. *NEJM*. 1999.
Burge PS. *Thorax*. 1999;54:267-268.
Renzard et al. Annual Meeting of the ATS; May 9-10, 2000; Toronto, Canada. Session B79.

ISOLDE

Burge PS et al. *Br Med J*. 2000;320:1297-1303.

- Inhaled Steroids in Obstructive Lung Disease in Europe study

ISOLDE

Burge PS et al. *Br Med J*. 2000;320:1297-1303.

- Patient Population:
- moderate to severe chronic COPD
- nonasthmatic,
- current or former smoker,
- aged 40-75
- FEV_1 after bronchodilator at least 0.8L and <85% predicted normal [mean was 50% ± 15%]
- FEV_1/FVC <70%

Burge PS et al. BMJ 2000;320:1297-1303

ISOLDE

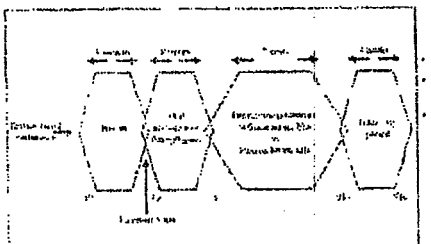
Burge PS et al. *Br Med J*. 2000;320:1297-1303

- Primary endpoints:
  - decline (mL/yr) in FEV_1 after bronchodilator
- Other key endpoints:
  - frequency of exacerbation
  - changes in health status
  - withdrawal because of respiratory disease
  - am serum cortisol concentration
  - adverse events

Burge PS et al. BMJ 2000;320:1297-1303

ISOLDE

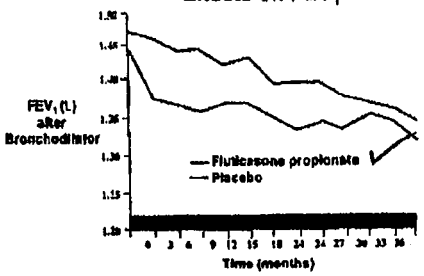
Burge PS et al. *Br Med J*. 2000;320:1297-1303



- N = 751
- Reversibility <10%
- Mean FEV_1: 55% at baseline

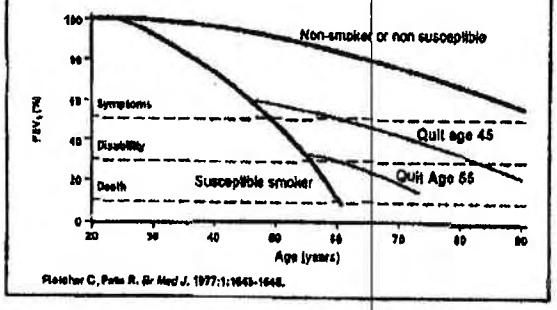
ISOLDE:

Effects on FEV_1



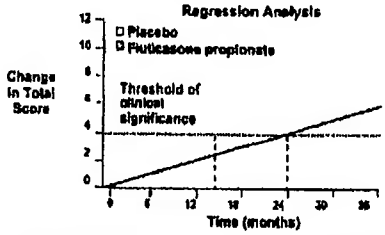
Burge PS et al. *Br Med J*. 2000;320:1297-1303

Decline in FEV1 Normal versus COPD Subjects



Fletcher C, Peto R. *Br Med J.* 1977;1:1645-1648.

ISOLDE: Change in SGRQ



An increase in score reflects a decrease in quality of life $P = .004$

Burge PS et al. *Br Med J.* 2000;320:1297-1303.

ISOLDE: Conclusions

Moderate-to-severe COPD: FP 1 mg daily:

- No significant difference in annual rate of ↓ in FEV1
- Median exacerbation rate ↓ by 25% vs PCB ($P < .028$)
- Fluticasone resulted in fewer withdrawals due to respiratory disease (25% vs 19%, $P = .034$)
- Reduced rate of decline in health status (St. George's)
- Numerically small but statistically sig. ↓ cortisol levels

Lung Health Study II

Connett. *Lung Health Study II Protocol.* 2000 ATS: Session L-4. Burge PS. *Thorax.* 1999. 54:287-288.

- **Multicenter**
  - Ten centers (9 U.S.; 1 Canada)
- **Triamcinolone 1200 µg/d vs placebo for 3 years**
  - Randomized, double-blind
- **Subjects (N = 1100; 90% smokers)**
  - FEV_1: mean 64%
  - FEV_1/FVC: 57%

Lung Health Study II

Connett. *Lung Health Study II Protocol.* 2000 ATS: Session L-4. Burge PS. *Thorax.* 1999. 54:287-288.

- FEV_1 deteriorated equally
- ICS group
  - BHR and dyspnea decreased
  - Fewer new respiratory symptoms ($P = .02$)
  - Fewer hospitalizations and clinic visits

Major ICS Trials Summary: Effect on FEV_1 and Exacerbations

Study	Treatment (µg/day)	Randomized Patients	Mean Δ FEV_1 (mL/year) * Placebo	ICS	Exacerbations Vs Placebo
ISOLDE	FP 1000 ✓	751	-39	-50	TE 25%(p=0.26)
Pepsero	FP 1000 ✓	281	-40	+150	ME/SE 60% vs 88% (p<.001)
Copenhagen LS	BUD 800	280	-42	-42	TE 4%(p: NS)
EUROSCOP	BUD 800	812	-59	-57	Not Available
Lung Health II	TAA1200	1100	-47	-44	TE No P value given

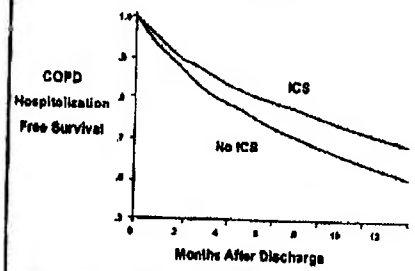
* Peppiee = mL/6 Months
TE = total exacerbations; SE = severe exacerbations; ME = moderate exacerbations

INHALED STEROIDS AND MORTALITY

Sin DD. Am J Respir Crit Care Med 2001; 164: 580

- 22,620 patients; ≥ 65 years of age hospitalized at leas once for COPD exacerbation 1992-1997
- COPD patients identified by administrative databases in Ontario
- Inhaled steroid used in 90 days post-hospital discharge: 51%
- Rx failure: death or hospitalization

Adjusted Probability of Hospitalization-free Survival



Adapted from Sin DD, Tu JV. Am J Respir Crit Care Med 2001;164:580-584

Impact of ICS in Elderly Patients with COPD: Relative Risk Reduction

- 26% relative reduction in combined risk for all-cause mortality and repeat hospitalization
- 24% (95% CI, 20% to 28%) reduced re-hospitalization
- 29% (95% CI, 22% to 35%) reduced mortality

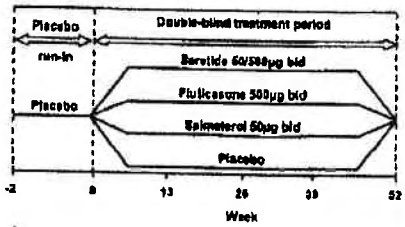
Impact of ICS in Elderly Patients with COPD

ICS reduced mortality & re-hospitalization regardless of:

- Age
- Sex
- Co-morbidity in COPD

Adjusted Risk*: Medications within 90-days Post-discharge

Fluticasone/Salmeterol in COPD: Tristan Study Design



(Tristan, GSK) data On File

Patient Entry Criteria

Inclusion Criteria

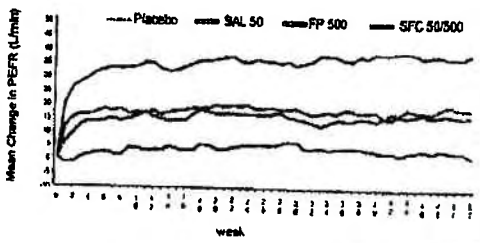
- COPD ERS definition
- Exacerbations in last 3 yrs
- Poor reversibility (< 10% predicted normal FEV_1)
- Pre-Bronchodilator FEV_1 25-70% predicted
- FEV_1/FVC < 70% predicted

Exclusion Criteria

- Current diagnosis of asthma, eczema, allergic rhinitis
- Systemic steroids, antibiotics or change in COPD medication in last 4 weeks

TRISTAN, GSK Data on file

Change in am PEF over weeks 1-52



Tristan, data On File

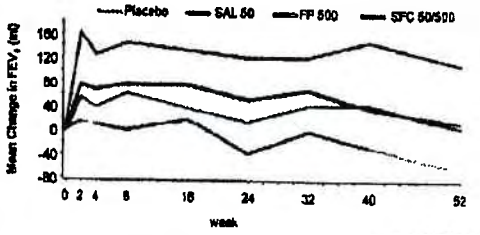
Change in am PEF over weeks 1-52

	n	BAL	Adj mean change	Treatment diff (SFC - comparator)	95% CI	p-value
Placebo	367	243	-0.4	32	26, 37	<0.001
SAL50*	370	235	15	17	11, 22	<0.001
FP500**	370	248	13	18	13, 24	<0.001
SFC50/500	363	247	31	-	-	-

* Treatment difference SAL50 vs placebo = 15 L/min (95% CI: 9, 20, p<0.001)
** Treatment difference FP500 vs placebo = 13 L/min (95% CI: 8, 18; p<0.001)

TRISTAN, data on file

Pre-dose FEV_1 Over Weeks 1-52



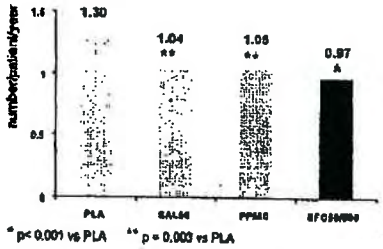
Tristan, data On File

Definitions of Exacerbations

- **Moderate**: Requiring treatment with antibiotics and/or oral corticosteroids
- **Severe**: Requiring emergency hospital treatment

TRISTAN, data on file

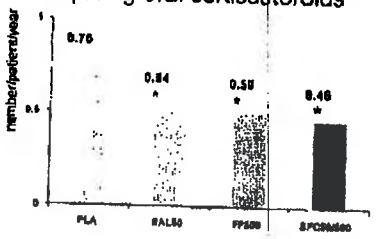
Moderate and/or Severe Exacerbations



* p< 0.001 vs PLA ** p = 0.003 vs PLA

Tristan, data On File

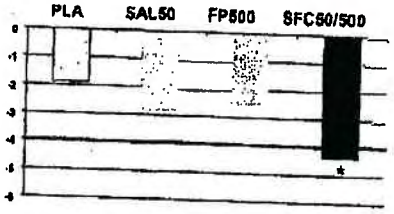
Moderate and/or severe exacerbations requiring oral corticosteroids



* p< 0.001 vs PLA

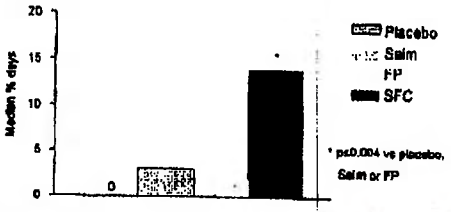
Tristan, data On File

SGRQ: Total Score at Endpoint



* p≤0.039 vs PLA and FP

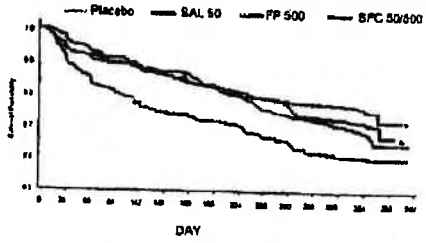
% days with no rescue medication



* p≤0.004 vs placebo, Salm or FP

Tristan, data On File

Time to Withdrawal Survival Distribution



Tristan, data On File

Most common drug-related adverse events

No. Patients (%)	Placebo (n=381)	Salmeterol (n=372)	FP (n=374)	SFC (n=358)
Any event	49 (14%)	46 (12%)	70 (19%)	58 (16%)
Candidiasis	5 (1%)	7 (2%)	31 (8%)	23 (6%)
COPD exacerbation	19 (5%)	8 (2%)	10 (3%)	9 (3%)
Oral inflammation/nausea	8 (2%)	3 (<1%)	3 (<1%)	4 (1%)
Cough/LRTI/URTI/ hoarseness	14 (4%)	15 (4%)	22 (6%)	18 (5%)
Headache/insomnia/vertigo	4 (1%)	10 (3%)	2 (<1%)	4 (1%)

TRISTAN, data on file

Overall summary of adverse events

No patients (%)	Placebo (n=381)	Salmeterol (n=372)	FP (n=374)	SFC (n=358)
Adverse event	283 (78%)	285 (76%)	302 (81%)	280 (80%)
Serious adverse event	54 (15%)	60 (16%)	55 (15%)	62 (17%)
Drug -related AE	49 (14%)	46 (12%)	70 (19%)	58 (16%)
Withdrawal due to AE	56 (15%)	56 (15%)	51 (14%)	41 (11%)

Tristan, data On File

Oral Corticosteroids

- Conflicting results in stable COPD
- May lead to systemic side effects
- Treatment of exacerbations
  - Reduced treatment failure rate
  - Improved subjective dyspnea
  - Rapid improvement in lung function and symptom scores
  - Reduced in-hospital days
  - Maximum benefit obtained during first 2 weeks of therapy

Thompson WH et al. Am J Respir Crit Care Med. 1996;154:407-412.
Davies L et al. Lancet. 1999;354:456-460.
Niewoehner D et al. N Engl J Med. 1999;340:1941-1947.

Take Home Messages

- The pathogenesis of COPD is complex, variable and incompletely understood
- Bronchodilators remain the mainstay of therapy
- A subset of patients with COPD are steroid responsive but there are no good predictors

Take Home Messages

- An inhaled steroid trial for 3 months or more is best way to establish steroid responsiveness
- FEV1 is not the only or best outcome to assess response to treatment for COPD patients

Critical Care & Pulmonary Consultants, P.C.
Physician List

Initials	Physician Name	Type of Physician
AO	Olson, Amy	Internist
AS	Sullivan, Andrew	Pulmonologist
BB	Benish, Elizabeth	Internist
BH	Ham, Beth	Internist
BSH	Shukert, Benjamin	Internist
CH	Howard, Clancy	Internist
CK	Kotaru, Chakradhar	Pulmonologist
DAB	Bartelt, David	Internist
DB	Barnes, David	Internist
DH	Harris, Daniel	Internist
DP	Pearson, Duane	Internist
FH	Hung, Fei	Pulmonologist
GM	Misky, Greg	Internist
JB	Batuello, Joe	Internist
JF	Forrester, Joseph	Pulmonologist
JM	Manheim, Jonathan	Internist
JUB	Bodnar, Judith	Internist
JY	Youngwerth, Jeanie	Internist
KF	Flippo, Korie	Internist
KL	Lo, Kar-Ming	Pulmonologist
KP	Polu, Krishna	Internist
KTD	Trampe-Decker, Kim	Internist
KW	Wallick, Kristin	Pulmonologist
LL	Letkomiller, Lorena	Internist
MD	Dickinson, Matthew	Pulmonologist
MF	Fessler, Michael	Pulmonologist
MH	Harris, Michelle	Internist
MN	Norden, Mark	Internist
NS	Nana-Sinkam, Pat	Pulmonologist
PS	Salja, Pushpasree	Internist
RG	Gopal, Ravi	Internist
SB	Bethel, Shauna	Pulmonologist
SC	Coiro, Susanna	Internist
SF	Fischer, Stacy	Internist
SH	Haugen, Scott	Internist
SO	Oosterveen, Scott	Internist
SP	Patel, Sanjiv	Pulmonologist
SS	Sharma, Surit	Pulmonologist

This material is for your information only. This information should not, under any circumstances, be utilized in any manner with healthcare providers.

project spirometry
The measurable difference in respiratory care

Dear GlaxoSmithKline Respiratory Sales Representative:

As the leader in asthma and COPD therapeutics, GlaxoSmithKline is continually committed to helping improve the quality of care respiratory patients receive in primary care and pediatric practices. This is the principle upon which the GSK Respiratory Institute was founded and the basis for the inception of the new initiative, *Project Spirometry*.

Accurate assessment of lung function in patients suspected of having chronic respiratory diseases such as asthma or COPD is crucial. Lung function testing allows for early diagnosis of subtle pulmonary findings and provides a concise record of a patient's progress and disease progression. Spirometry is one of the most accurate tools for assessing lung function.

At one time, spirometers were bulky, difficult-to-use instruments relegated to the specialist's practice; in the past decade, improved spirometers have come on the market. The newer spirometers utilize two key values and one critical ratio making lung function assessment easier. Now spirometry is accessible to primary care and pediatric practices and offers the opportunity to improve respiratory care in this setting.

Project Spirometry provides practices with the unique opportunity to experience the benefits of these newer spirometers. Willing primary care and pediatric practices can receive a 60-day trial of a spirometer plus training and educational resources to help them appropriately utilize spirometry. This will allow physicians and other healthcare providers to experience firsthand the benefits that spirometry can bring to their respiratory patients.

In order for *Project Spirometry* to be a success, you must become a *Master of Spirometry*, possessing the ability to diligently communicate the benefits of this important program to physicians. The program contained herein, *Master of Spirometry*, is designed to give respiratory sales representatives the basics of spirometry.

Master of Spirometry is divided into 3 self-study modules:

Module 1: *Spirometry Essentials—A Comprehensive Master's Manual* provides a comprehensive introduction to lung function evaluation, normal and abnormal lung function, and applied spirometry.

Module 2: *Spirometry Reference Compendium* provides a review of the key clinical literature related to the use of office spirometry. This module will enable you to use clinical data and protocols to address clinicians' questions and concerns about spirometry and *Project Spirometry*.

Module 3: *Project Spirometry Policies and Business Guidelines* explains the program rules and requirements. Updated GSK policies and guidelines on sales representative activities related to *Project Spirometry* are also included. This module reviews the agreements by which GSK Sales Representatives and participating practices will need to abide.

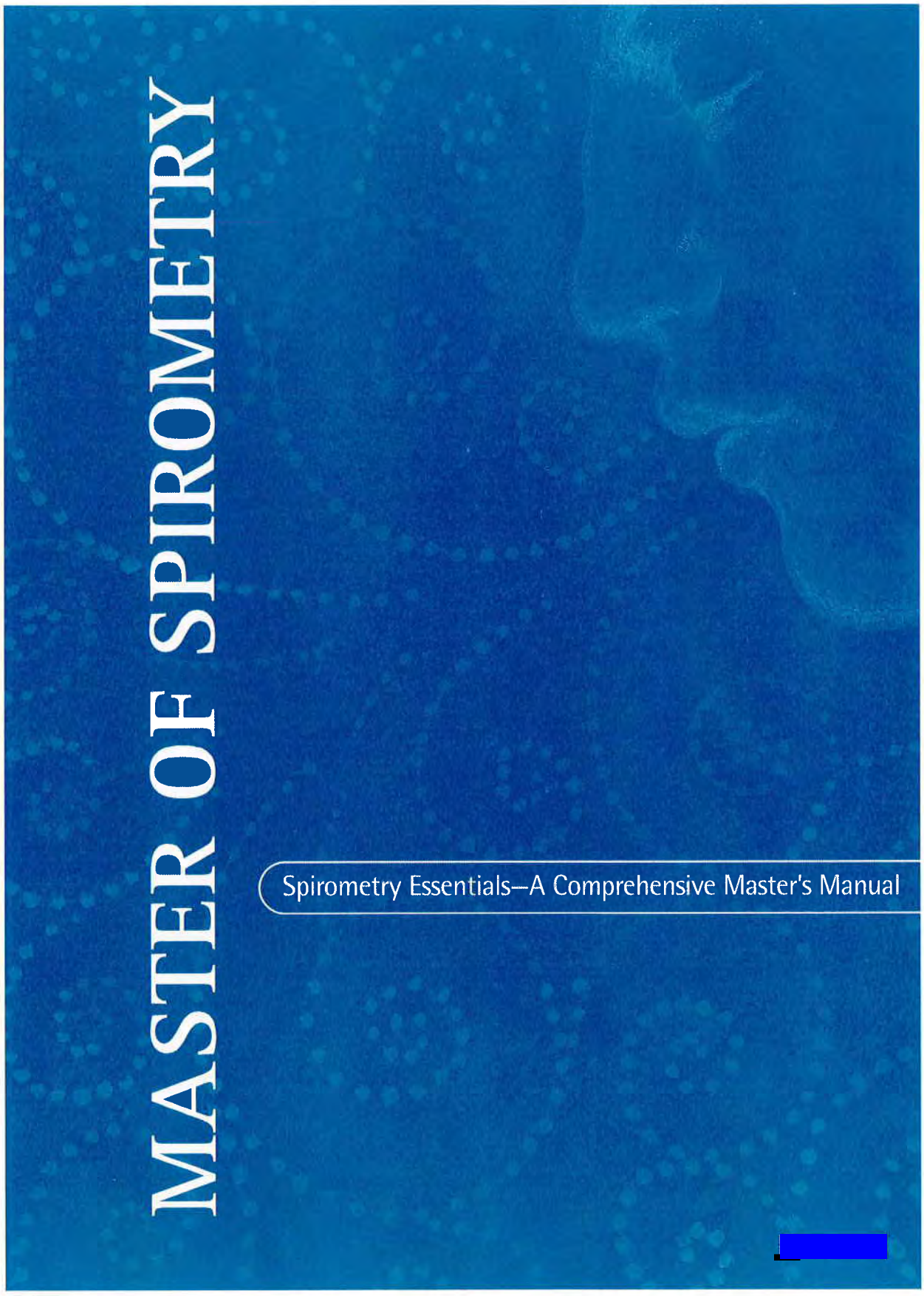
After you have completed the *Master of Spirometry* training program, you will have the opportunity to educate healthcare providers on *Project Spirometry* and place spirometers in practices, helping to enhance the quality of respiratory care.

The GSK Respiratory Institute thanks you for your participation in *Project Spirometry* and your contribution in helping to improve respiratory care nationwide.

Sincerely,

Elizabeth Mosher Bruce Cox Chris Phillips

THE RESPIRATORY INSTITUTE


MASTER OF SPIROMETRY
Spirometry Essentials—A Comprehensive Master's Manual